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THE ROLE OF GENE POLYMORPHISMS IN METABOLIC SYNDROME, COGNITIVE AND PSYCHOSOMATIC DISORDERS

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Abstract: Metabolic disorders such as obesity, insulin resistance, hypertension and dyslipidemia increase the risk of cardiovascular diseases as well as cognitive and psychosomatic disorders. With the increasing proportion of the elderly population, age-related cognitive decline, defined as a gradual decline in cognitive abilities during the aging process, has emerged as an important public health problem. Genetic determinants of cognitive and psychosomatic disorders in individuals with metabolic syndrome include a large number of genes involved in the regulation of inflammation, metabolism, neuroplasticity and stress. Studies confirm that cognitive impairment in the elderly population is mostly associated with various factors such as environment, lifestyle, metal exposure, some genetic polymorphisms and diseases. The influence of genetic factors in the mechanism of development of cognitive and psychosomatic disorders in metabolic syndrome may help to understand the underlying mechanisms of the disease by identifying genetic biomarkers that indicate susceptibility to the disease. It will also provide the opportunity to select patients for monitoring and follow-up of treatment progress. It may therefore help address the challenges of early diagnosis, screening and prognosis assessment in patients with cognitive impairment with metabolic syndrome.

Key words: Metabolic syndrome, cognitive disorders, gene polymorphisms, psychosomatic disorders

Метаболизмдік синдром кезіндегі когнитивтік және психосоматикалық бұзылыстардың ген полиморфизмдердің рөлі

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Аңдатпа: Семіздік, инсулинге төзімділік, гипертония және дислипидемия сияқты метаболизмдік бұзылыстар жүрек-қан тамырлары ауруларының, сондай-ақ когнитивтік және психосоматикалық бұзылулардың қаупін арттырады. Егде жастағы тұрғындардың үлес салмағының артуына байланысты, қартаю процесі кезінде когнитивтік қабілеттердің біртіндеп төмендеуі ретінде анықталған жасқа байланысты когнитивтік құлдырау маңызды қоғамдық денсаулық сақтау проблемасы ретінде пайда болды. Метаболизмдік синдромы бар адамдардағы когнитивтік және психосоматикалық бұзылыстардың генетикалық детерминанттары қабынуды, метаболизмді, нейропластиканы және стрессті реттеуге қатысатын гендердің үлкен санын қамтиды. Зерттеулер егде жастағы популяциядағы когнитивтік бұзылыстар көбінесе қоршаған орта, өмір салты, металл әсерлері, кейбір генетикалық полиморфизмдер сияқты әртүрлі факторлармен байланысты екенін растайды. Метаболизмдік синдромы бар адамдардағы когнитивтік және психосоматикалық бұзылыстардың даму механизміне генетикалық факторлардың әсері ауруға бейімділігін көрсететін генетикалық биомаркерлерді анықтау арқылы аурудың негізгі механизмдерін түсінуге көмектеседі. Ол сондай-ақ емдеу барысын бақылау және бақылау үшін пациенттерді таңдау мүмкіндігін береді. Сондықтан ол метаболизмдік синдромы бар адамдардағы

когнитивтік бұзылыстарды анықтау науқастарда ерте диагностика, скрининг және болжамды бағалау мәселелерін шешуге көмектеседі.

Түйін сөздер: Метаболикалық синдром, когнитивтік бұзылыстар, гендік полиморфизмдер, психосоматикалық бұзылыстар

Роль полиморфизма генов в метаболическом синдроме, когнитивных и психосоматических расстройствах

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Аннотация: Метаболические нарушения, такие как ожирение, инсулинорезистентность, гипертония и дислипидемия, увеличивают риск сердечно-сосудистых заболеваний, а также когнитивных и психосоматических расстройств. С увеличением доли пожилого населения возрастное когнитивное снижение, определяемое как постепенное снижение когнитивных способностей в процессе старения, стало важной проблемой общественного здравоохранения. Генетические детерминанты когнитивных и психосоматических расстройств у лиц с метаболическим синдромом включают большое количество генов, участвующих в регуляции воспаления, метаболизма, нейропластичности и стресса. Исследования подтверждают, что когнитивные нарушения у пожилых людей в основном связаны с различными факторами, такими как окружающая среда, образ жизни, воздействие металлов, некоторые генетические полиморфизмы и заболевания. Влияние генетических факторов на механизм развития когнитивных и психосоматических расстройств при метаболическом синдроме может помочь понять основные механизмы заболевания путем выявления генетических биомаркеров, которые указывают на восприимчивость к заболеванию. Это также даст возможность отбирать пациентов для мониторинга и наблюдения за ходом лечения. Таким образом, это может помочь решить проблемы ранней диагностики, скрининга и оценки прогноза у пациентов с когнитивными нарушениями при метаболическом синдроме.

Ключевые слова: Метаболический синдром, когнитивные расстройства, полиморфизмы генов, психосоматические расстройства

Introduction

Metabolic syndrome (MS) is one of the most pressing problems of modern medicine. MS is one of the most urgent problems of modern medicine. Cognitive dysfunction in MS is not only a medical but also a social problem of our time [1]. medical, but also social problem of our time, since impaired thinking processes significantly reduce the quality of life of patients, and in case of prolonged course leads to the development of dementia and complete social maladaptation. Identification of causes and mechanisms of development of cognitive dysfunction in patients with MS can be the basis for the development of pathogenetically grounded pathogenesis of cognitive dysfunction in patients with MS [2]. pathogenetically grounded methods of prevention and correction of mnesticco dysfunction in MS patients and correction of mnestic-intellectual disorders. MS plays a significant role in accelerating the development and progression of cardiovascular disease associated with atherosclerosis. One of the important target organs in MS is the brain. It is known that the risk of brain strokes in persons with MS is 6-7 times higher than in the general population [3]. Metabolic disorders including obesity, insulin resistance, hypertension and dyslipidemia increase the risk of cardiovascular disease as well as cognitive and psychosomatic disorders. Genetic factors play an important role in the pathogenesis of these conditions. The most studied cognitive functions in metabolic syndrome are attention, memory, and executive functions.

Because attention prepares the ground for higher-level cognitive processes, attention impairments limit the success of many cognitive functions [4]. With increasing age, the risk of cognitive impairment gradually increases as the organs and functions of the body gradually deteriorate, the functional structure of the brain atrophies, and cognitive function also gradually declines. As a person ages, the quality of cognitive function becomes an increasingly important topic. Studies have confirmed that cognitive impairment in the elderly population is mainly related to various factors such as environment, lifestyle, metal exposure, some genetic polymorphisms and diseases. According to the results of numerous large independent epidemiological studies, an increase in systolic blood pressure in middle age statistically significantly increases the risk of developing cognitive impairment after 60 years. If a patient has several vascular diseases, the risk of developing cognitive impairment increases [12].

Genetic polymorphisms associated with one-carbon metabolism disorders may be a risk factor not only for somatic and neurological diseases, but also for psychosomatic disorders. A genome-wide association study has identified many single-nucleotide polymorphisms (SNPs) of genes involved in the regulation of energy processes, as well as their association with obesity, high body mass index, and the risk of developing cognitive impairment [13]. In the development of cognitive disorders in patients with metabolic syndrome, the contribution of genetic factors to the development of cognitive dysfunction is discussed in the literature.

The aim of this literature review was to review the current evidence on neurologic and genetic biomarkers contributing to the development of cognitive impairment in metabolic syndrome. Some genetic markers of cognitive impairment, such as polymorphisms of some genes. Scopus, PubMed, Google Scholar and Web of Science, the main and most well-known information databases of biomedical literature, will be used to prepare the review. The review includes highly cited English language publications between 2020 and 2025. The following gene polymorphisms were studied as part of the performed molecular genetic study: ApoE, FTO and MC4R genes.

ApoE gene

Genetic polymorphisms may determine variability in cognitive impairment in patients with metabolic syndrome [14]. The importance of genetic influences on cognitive impairment has long been recognized. Genetic association analyses have now identified 709 genes that are significantly associated with overall cognitive function. Among them, the gene encoding the apolipoprotein ApoE is located on chromosome 19 and has three isoforms, ApoE 2, ApoE 3, and ApoE 4, which are expressed by the ε2, ε3, and ε4 alleles, respectively. APOE is well recognized for its major role in cognitive decline in the elderly [5]. ApoE may affect the metabolic deposition of amyloid β (Aβ) peptides, lipid metabolism, inflammatory response and other mechanisms that cause cognitive impairment in the body through increased toxicity or loss of neuroprotective effects. Zejan et al, investigated that ApoE loci rs7412, rs7259620 and rs405509 were associated with cognitive impairment in the elderly [1]. APOE may also affect cognitive abilities in normal aging. According to the GWAS study of cognitive testing such as memory and perceptual speed, Shilna et al. found that genome-wide APOE was significantly correlated with age-related cognitive decline [6]. The effect of APOE-ε 4 carrier status on longitudinal cognitive decline in Parkinson's disease was investigated in the CamPaIGN cohort (n=107) over 5 years from diagnosis, and no evidence of association with the rate of change in MMSE scores, age-related cognitive decline, or incidence of dementia was found [8]. Various studies have shown the influence Apo-ε4 for memory, information transfer speed and on other aspects of cognitive functions. Some researchers did not note demographic data such as gender and age on the association between ApoE polymorphism and cognitive impairment. One prospective cohort study by Christine Jaffe of 1750 women aged 65 years and older found that ApoE E ε4 was associated with cognitive decline in community-dwelling, non-demented women [19].

FTO gene

The FTO gene is expressed in various tissues: liver, muscle tissue, adipocytes, pancreatic β-cells, but to a greater extent in the hypothalamus. FTO plays an important role in regulating energy homeostasis, body weight and food intake [19]. The most studied SNP of the FTO gene is rs9939609, in which either thiamine (T) or adenine (A) can be present in the first intron of the gene (chromosome 16, position 53820527) [15]. The relationship between FTO gene SNP and T2DM was first demonstrated in 2007 in a GWAS study. It was later found that this relationship is realized through the effect on BMI. Frayling et al. found that carriers of the A allele of the FTO gene (rs9939609) had a higher body weight and an increased risk of developing obesity (OR 1.7) compared with individuals homozygous for the T allele [16]. In addition to the relationship between the FTO gene and MS, a number of researchers also find an association between FTO and various components of MS: plasma glucose levels, lipoprotein and triglyceride levels. The authors emphasize that this relationship was observed in study participants over a long observation period (from childhood to old age). According to Zhang et al (2023), in a sample of 8364 white and 2083 African American men and women with no clinical history of stroke, a significantly greater mean change in delayed word recall test performance was associated with 2 of the 4 FTO single nucleotide polymorphisms examined (rs9939609, rs805136, rs17817449, and rs1421085) in whites but not in African Americans ($p \leq 0.002$). The association of FTO polymorphisms with cognitive changes was independent of potentially confounding clinical and demographic variables including age, gender, education, diabetes, hypertension, and body mass index [7]. Saunder's meta-analysis of over 12,000 participants reported an association between rs9939609 of the FTO gene and the risk of cognitive impairment [17]. Polymorphism of the FTO gene rs9969309 is associated not only with AO, but also with other components of MS, such as hyperglycemia and hypertension. Moreover, carriage of the A-allele of the FTO gene may be associated with the presence of several components of MS at once [18].

MC4R gene

Alterations in the gene encoding the melanocortin 4 receptor (MC4R) are the most common genetic cause of obesity in humans, and obesity itself has been found to be independently associated with psychosomatic disorders, including depression. A common single nucleotide polymorphism (SNP) of the rs17782313 gene near MC4R may be significantly associated with increased total energy intake and dietary fat content. In addition to the association of the MC4R gene with obesity and the association of the C allele variant of rs17782313 with BMI, studies have found an association of this gene with depressed mood and compulsive overeating. In a study by Hajmur et al., it was shown that the interaction of mental stress and energy intake with MC4R minor allele genotype may increase the risk of obesity in Korean adults [10]. However, since research on the association between the MC4R gene and depression is very limited and there have been no studies on the interaction of the MC4R gene with dominant eating patterns and depression, this study was the first to attempt to examine their interaction. The MC4R polymorphism (rs17782313) shows a direct association between depressive illness and greater adherence to unhealthy eating behaviors in individuals with the CC allele of the MC4R gene. The results of this study suggest that the interaction of MC4R variants between individuals and high UDP intake may play an important role in the development of depression. The rs17782313 polymorphism near the MC4R gene was also found to be associated with obesity among European adults. The rs17782313 polymorphism in the MC4R gene and its association with obesity were first described in 2008 [11].

Conclusion

Cognitive aging involves multiple complex pathogenesis including genetic and environmental factors. With an ever-increasing population of older adults, age-related cognitive decline, which is characterized as the gradual decline of cognitive abilities during aging, has proven to be a giant public health problem. As genetic information has become increasingly important for studying the biological mechanisms of cognitive decline, the search for genetic biomarkers of

cognitive aging has attracted much attention. The presented review highlights the main pathways of cognitive impairment in diabetes mellitus and indicates the genes associated with them. Studying these genetic predictors may make it possible to predict the development of cognitive and psychosomatic disorders in patients with MS.

Genetic predictors of cognitive and psychosomatic disorders in individuals with metabolic syndrome encompass multiple genes involved in the regulation of inflammation, metabolism, neuroplasticity, and stress. These findings offer prospects for personalized medicine and preventive strategies that can significantly improve patients' quality of life. Gene polymorphism has complex effects on physiological and psychological processes, contributing to predisposition to metabolic syndrome, cognitive and psychosomatic disorders. Studying these interactions opens up prospects for personalized medicine, including prevention and targeted therapy.

Therefore, it is important to search for genetic markers associated with MS, which will help to reveal the mechanisms of regulation of neurological disorders associated with cognitive and psychosomatic disorders, and can help select patients from a high-risk group and assess qualitative and quantitative changes against the background of different genotypes, which will allow not only to treat, but also to effectively prevent MS and its complications. Some scientists also believe that one direction for future research is to use cognitive abilities to assess polygenic risks for predicting MS in accordance with the feedback hypothesis, according to which people with lower cognitive abilities are more likely to develop components of MS.

Conflict of interest. The authors declare no conflict of interest.

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